PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

GODDARD, Carolyn
GlaxoSmithKline
Corporate Intellectual Property (CN
980 Great West Road
Brentford Middlesex TW8 9GS
GRANDE BRETAGNE

GlaxoSmithKline
Corporate IP
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NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	03.07.2006
Applicant's or agent's file reference CJG/PB60780	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2005/000939	10.03.2005	12.03.2004

Applicant
GLAXO GROUP LIMITED

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Rossi, C Tel. +31 70 340-3322

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference CJG/PB60780	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/GB2005/000939	International filing date *(day/month/year)* 10.03.2005	Priority date *(day/month/year)* 12.03.2004

International Patent Classification (IPC) or national classification and IPC

INV. C07D223/16 C07D405/12 C07D401/12 C07D417/12 C07D409/12 C07D413/12 C07D403/12 C07D495/04 C07D409/14 C07D513/04 C07D471/04 C07D413/04 C07D401/04 C07D405/04 C07D417/04 C07D405/14 C07D401/14 C07D413/14 C07D417/14 C07D487/04 A61K31/55 A61P25/00

Applicant

GLAXO GROUP LIMITED

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

- ☒ Box No. I Basis of the report
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
16.08.2005	03.07.2006

Name and mailing address of the international preliminary examining authority:

European Patent Office - P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
Fax: +31 70 340 - 3016

Authorized officer

Seitner, I

Telephone No. +31 70 340-2389

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2005/000939

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-75 as originally filed

   Claims, Numbers

   1-9 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 7 (with respect to industrial applicability)

because:

☒ the said international application, or the said claims Nos. 7 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*.

☐ no international search report has been established for the said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2-9
	No:	Claims	1
Inventive step (IS)	Yes:	Claims	2-9
	No:	Claims	1
Industrial applicability (IA)	Yes:	Claims	1-6,8-9
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 7 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 96/05194 A (DR. KARL THOMAE GMBH) 22 February 1996 (1996-02-22)

D2: EP-A-0 612 741 (DR. KARL THOMAE GMBH) 31 August 1994 (1994-08-31)

D3: WO 2004/018432 A (ELI LILLY AND COMPANY; GADSKI, ROBERT, ALAN; HIPSKIND, PHILIP, ARTHUR;) 4 March 2004 (2004-03-04)

V.1. Novelty:

Documents D1 and D2 disclose compounds (see in D1: page 76, compound (9), page 93, example 10; in D2: page 45, examples (29) and (31)) falling within the scope of the present general formula (I).

Applicant argues that the group R^2 cannot be substituted by a carboxylic or ester group.

However, according to claim 1, R^2 may be substituted by $-C_{1-6}alkyl-COR^5$ with R^5 being hydroxy or $C_{1-6}alkoxy$ (see page 76, lines 26-27 and 36).

Thus, the compounds of D1 and D2 correspond to present formula (I) of claim 1, when R^2=-heterocyclyl-X-C_{3-8}cycloalkyl with X being a bond, the heterocyclyl of R^2 being

substituted by =O and the cycloalkyl of R^2 being substituted by -C_{1-6}alkyl-COR^5 (with R^5=hydroxy or C_{1-6}alkoxy).

Therefore, the subject-matter of claim 1 is not novel over the prior art (Article 33(2) PCT).

The compounds of claim 2 and the pharmaceutical use of compounds of formula (I) for the treatment of neurological disorders have not been disclosed in the prior art.

Therefore, the subject-matter of claims 2-9 is novel (Article 33(2) PCT).

V.2. Inventive Step:

The subject-matter of claims 1-9, in as far as novel, is considered as involving an inventive step in the sense of Article 33(3) PCT:

Document D3 is regarded as being the closest prior art the subject-matter of the present application and discloses (see page 39: example 32; page 37: example 20; page 1; claims 9-15) benzazepine derivatives which are histamine receptor antagonists for the treatment of Alzheimer disease, mood and attention adjustments, cognitive deficiencies, obesity, dizziness, schizophrenia, epilepsy, sleeping disorders, narcolepsy and motion sickness.

The general formula (I) of claim 1 differs from these known compounds in that the nitrogen atom of the benzazepine ring is substituted by cycloalkyl (corresponding to the definition of R1) and the phenyl ring of the benzazepine ring is substituted by aryl, heterocyclyl, heteroaryl (corresponding to the definition of R2). In the compounds of D3 the nitrogen atom is substituted by cycloalkyl-methyl and the phenyl ring by piperidinyl-alkoxy.

The problem to be solved by the present invention may therefore be regarded as the provision of further histamine receptor antagonists for the treatment of neurological disorders.

In view of the teaching of the prior art, the skilled person had no incentive to undertake above mentioned modifications on the compounds known from D3 when searching for further histamine receptor antagonists for the treatment of neurological disorders.

Hence, the novel subject-matter of claim 1 and the subject-matter of claims 2-9 is considered as involving an inventive step (Article 33(3) PCT).

V.3. Industrial Applicability:

The present application relates to compounds which are useful for the treatment of neurological diseases and the subject matter of claims 1-6 and 8-9 is therefore considered as industrially applicable (Article 33(4) PCT).

For the assessment of the present claim 7 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.